SPECIFICATION

Kindly add enclosed abstract page 37 to the present application.

IN THE CLAIMS

Kindly substitute enclosed amended claim pages 35 and 36 for claim page 35, as originally filed.

The applicant has amended independent claims 1 and 5, has cancelled original claims 6-8, and has added new claims 2, 3, 7, 9 and 11-15.

The remaining claim numbers and dependancies have been amended accordingly.

A marked up copy of the claims showing the amendments made is enclosed, together with clean replacement claim pages 35 and 36.

REMARKS

Claim Amendments Relating to Nitric Oxide Agonists

The applicant has amended or added claims 1, 3, 5, 7, 9, 12, 13 and 15 to include methods or compositions involving nitric oxide agonists. Support for these claims can be found in the specification and particularly at page 8, line 12, and page 10, line 14.

Claim Objections

The applicant has amended claim 1, pursuant to the Examiner's objection, to make reference to a mammalian patient to whom the compound is administered.

Claim 8 as originally filed has been cancelled.

The applicant has amended claim 1 to be directed to a method of increasing insulin sensitivity by administering an effective amount of a nitric oxide donor or nitric oxide agonist compound. This amendment was made for reasons unrelated to the art cited against this claim by the Examiner. Argument with respect to the art cited by the Examiner follows.

35 USC § 102

Original Claims 1-4 (Corresponding to Amended Claims 1, 2, 4, 6 and 8)

Petrie *et al.* discloses the separate administration of either a nitric oxide synthesis inhibiting compound (L-NMMA), a stimulator of nitric oxide synthase (acetylcholine), or a nitric oxide donor (sodium nitroprusside) to the brachial artery, for delivery directly to vasculature within skeletal muscle.

Petrie reports a correlation between reduced insulin sensitivity and the response to L-NMMA, an inhibitor of nitric oxide synthase, but no correlation between insulin sensitivity and responses to the stimulator of nitric oxide synthase (acetylcholine) or the nitric oxide donor (sodium nitroprusside). (See Results section third and fourth sentences before the end, as well as the final line in the "Methods and Results" portion of the Abstract.)

As no correlation between insulin sensitivity and the response to a stimulator of nitric oxide synthase, nitric oxide donor or nitric oxide agonist was shown, Petrie does not teach a method of increasing insulin sensitivity. In fact, Petrie's reported failure to obtain an increase in insulin sensitivity underscores the surprising and novel nature of the present invention.

Thus, the applicant submits that claim 1, and dependent claims 2 through 9, are not anticipated by Petrie *et al.*

Claims 5-8 (Corresponding to Amended Claims 10 and 11)

The applicant has amended original claim 5 (amended claim 10) to more clearly indicate that the pharmaceutical composition of interest comprises, *inter alia*, an amount of a nitric oxide donor compound effective to cause an increase in nitric oxide in the liver.

The applicant has further amended original claim 5 (amended claim 10) to indicate that the compound is a nitric oxide donor compound. This amendment was made for reasons unrelated to the art cited against these claims by the Examiner. Argument with respect to the art cited by the Examiner follows.

The references cited by the Examiner with respect to original claims 5 through 7 (corresponding to amended claims 10 and 11) disclose various compositions including stimulants of nitric oxide synthesis, or nitric oxide donors, with pharmaceutically acceptable carriers. However, these references do not teach amounts of the nitric oxide producing compounds effective to cause an increase in nitric oxide in the liver.

Thus, the applicant submits that claim 10 as amended, and dependent claim 11 are novel and non-obvious in light of the cited art.

35 USC § 103

The applicant submits that Petrie *et al.* is inapplicable to the claims as amended for the reasons previously discussed. In particular, Petrie neither teaches nor suggests a role for nitric oxide donors or nitric oxide agonists in increasing insulin sensitivity. Thus, the applicant submits that the pending claims are non-obvious in light of the cited art.

The applicant has received a form entitled "Attachment for PTO-948" relating to drawing changes. However, the applicant is not aware of any requisition with respect to

the drawings pending in this application. If such a requisition is outstanding, the applicant respectfully requests that the Office notify the applicant as soon as possible.

An Information Disclosure Statement in respect of this United States Patent Application will be submitted under separate cover. The Information Disclosure Statement merely restates the references listed on pages 32 to 34 of the specification, and in the International Search Report as well as US 5,561,165 of Lautt, previously cited by the Examiner.

The applicant has added a further independent claim by amendment. Kindly charge all applicable fees at the small entity rate to our deposit account 13-2400. Notification of charges made would be appreciated.

Favourable reconsideration and allowance of this application are respectfully requested.

Should the Examiner believe however that additional amendments to the claims may be required to secure allowance of this application, she is invited to telephone Robert G. Hirons (Registration No. 24666) at the below-noted number to facilitate further prosecution of this application.

This response is being forwarded to you via facsimile transmission to the Patent Examination Section (703) 308-4556, with the original following by courier and we trust this will be in order.

Respectfully Submitted,

LAUTT, Wayne

By: _____

Mitchell B. Charness, Reg. No. 46416

Place: Ottawa, Ontario, Canada

Date: November 28, 2001

Tele No.: (613) 236-1995

ABSTRACT OF THE DISCLOSURE

There is provided a method of increasing insulin sensitivity in a mammalian patient by administering an effective amount of a nitric oxide donor or nitric oxide agonist compound to the liver. Also provided is a pharmaceutical composition useful to cause an increase in nitric oxide in the liver of a patient in need thereof. The composition comprises an amount of a compound effective to cause an increase in nitric oxide in the liver, and a pharmaceutically acceptable carrier.

CLAIMS:

1. A method of increasing insulin sensitivity in a mammalian patient by: administering to the patient an effective amount of a nitric oxide donor or nitric oxide agonist compound.

2. The method according to claim 1, wherein the compound is a nitric oxide donor compound.

3. The method according to claim 1, wherein the compound is a nitric oxide agonist compound.

4. The method according to claim 2, wherein said administering step further includes orally administering the compound.

5. The method according to claim 3, wherein said administering step further includes orally administering the compound.

6. The method according to claim 2, wherein said administering step further includes injecting the compound.

7. The method according to claim 3, wherein said administering step further includes injecting the compound.

8. The method according to claim 2, wherein said administering step further includes delivering the compound through a pump system directly into the portal vein.

9. The method according to claim 3, wherein said administering step further includes delivering the compound through a pump system directly into the portal vein.

Rule 126 12 ~~10.~~ A pharmaceutical composition useful to cause an increase in nitric oxide in the liver of a patient in need thereof, said composition comprising an amount of a nitric oxide donor compound, said amount being effective to cause an increase in nitric oxide in the liver, and a pharmaceutically acceptable carrier.

A3 Cont

13 ~~11.~~ The pharmaceutical composition of claim 12 ~~10~~, wherein said donor is adapted to preferentially release nitric oxide in the liver.

Rule 126

Sub C1

14 ~~12.~~ A pharmaceutical composition useful in increasing insulin sensitivity in a mammalian patient, said composition comprising an effective amount of a nitric oxide agonist, and a pharmaceutically acceptable carrier.

Rule 126

15 ~~13.~~ A kit comprising:

Rule 126

at least one of a nitric oxide donor or a nitric oxide agonist; and,

instructions for the administration of said nitric oxide donor or nitric oxide agonist to ameliorate the symptoms of insulin resistance.

Rule 126

16 ~~14.~~ The kit of claim 15 ~~13~~, including a nitric oxide donor.

17 ~~15.~~ The kit of claim 15 ~~13~~, including a nitric oxide agonist.

Rule 126